# HUMAN DRUG CGMP NOTES

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**(A Memo on Current Good Manufacturing Practice Issues on Human Use Pharmaceuticals)**

**Issued By: The Division of Manufacturing and Product Quality, HFD-320**
**Office of Compliance**
**Center for Drug Evaluation and Research**

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(Your input requested)

**MOTISE'S NOTEBOOK:**

Welcome to another edition of Human Drug CGMP Notes, our periodic memo on CGMP for human use pharmaceuticals. Your FAX FEEDBACK responses are still great and we especially appreciate your suggested topics for coverage. You need not, however, limit the dialog to FAX FEEDBACK. Feel free to call, write, or send us e-mail, as several of you have done. We also welcome brief articles FDAers may wish to contribute. Subjects should be CGMP related and would be especially valuable if they address emerging new technologies.

As a reminder, although this document is fully releasable under the Freedom of Information Act, our intended readership is FDA field and headquarters personnel. Therefore, we cannot extend our distribution list for the paper edition to people outside the agency. The primary purpose of this memo is to enhance field/headquarters communications on CGMP issues in a timely manner. This document is a forum to hear and address your CGMP questions, update you on CGMP projects, and help you apply real life situations to existing policy and enforcement documents. This publication does not supplant existing policy development/issuance mechanisms.

Appended to each edition of the memo is a *FAX FEEDBACK* sheet to make it easier for us to communicate. In addition to FAX (at 301-594-2202), you can reach us by interoffice paper mail, using the above address, by phone at (301) 594-0098, or by electronic mail.

If you would like to receive an electronic version of this document via electronic mail, let us know (see the check-off line in FAX FEEDBACK).

Thanks!

*Paul J. Motise*

**POLICY QUESTIONS:**

***Does the FDA Modernization Act limit FDA's OTC records inspection authority to only those records created after 2/19/98?***

References: U.S. Food, Drug and Cosmetic Act, Section 704(a)(1), as amended by the Food and Drug Administration Modernization Act (FDAMA) at Section 751; Compliance Policy Guide 7151.02, Sec 130.300, FDA Access to Results of Quality Assurance Program Audits and Inspections.

No. OTC records created before 2/19/98 (the effective date of this part of the revised law) are not grandfathered. The FD&C Act now authorizes investigators to inspect records pertaining to over-the-counter, as well as prescription, drugs. The FDAMA amended 704(a)(1) by striking "prescription drugs" each place it appears and inserting "prescription drugs, nonprescription drugs intended for human use,".

Investigators should not, however, routinely ask to review OTC self audit reports (a firm's own audits and inspections of its operations), although FDA reserves the right to review such records.

This is consistent with CPG 7151.02, and the Congressional Joint Explanatory Statement of the Committee of Conference regarding the FDAMA.

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***Is skip-lot testing, for batch release purposes, acceptable under CGMPs?***

Reference: 21 CFR, Subpart I, Laboratory Controls, 211.165(a), Testing and release for distribution

No. CGMPs must be followed all of the time, and not just sometimes, as would be the case with skip-lot testing.

At section 211.165(a), the CGMP regulations specify that: FOR EACH BATCH OF DRUG PRODUCT, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. (Emphasis added)

If only every other lot is tested, or if only one out of every ten lots manufactured is tested, then this would be in violation of 211.165.

The argument for skip-lot testing is that for a validated manufacturing process, testing of each lot shouldn't be necessary. If that were true then there should never be any batch failures or drug product recalls, and we all know that batch failures and recalls are not uncommon. More importantly, though, there is always the possibility of human error or equipment failure, and that is the reason why all manufactured batches must undergo laboratory testing prior to release; things can and do go wrong, such that the process applied to a given batch may differ from the validated process.

Basic to the CGMP approach is the concept of checks and balances to build quality into a product. Omitting end product testing reduces such checks and can increase the likelihood of distributing a defective product. For instance, if (under a vendor validation program) only an identification test is conducted for what is, in fact, a substandard raw material, and a batch of finished drug product incorporating that material was selected as a skip-lot, then there would be a higher probability that the problem would go undetected.

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***If a firm's only operation is performing finished packaging operations for bulk tablet and capsule drug products, must it still maintain separate facilities and equipment for packaging penicillin products?***

Reference: 21 CFR Sections 211.42.(d), Design and construction features [Buildings and Facilities], 211.46(d), Ventilation, air filtration, air heating and cooling, and 211.176, Penicillin contamination

Yes. The CGMP regulations explicitly require that operations relating to the manufacture, processing and packaging of penicillin be performed in facilities that are separate from those facilities used for other drugs. The regulations also require separate air-handling systems in facilities used for penicillin products. Furthermore, if a reasonable possibility exists that a non-penicillin drug product has been exposed to cross-contamination with penicillin, CGMPs require that the non-penicillin drug be tested for the presence of penicillin. The CGMPs make no exceptions from the foregoing for operations that are limited to repackaging solid oral dosage forms.

It should be noted that the requirement for separate facilities does not necessarily mean that operations relating to penicillin products must be conducted in separate buildings from other drugs. A separate area dedicated to penicillin products within a larger facility may be acceptable if penicillin containment can be established and validated.

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***Is it acceptable under section 211.176 to release products to market as long as the products are tested and no penicillin is found?***

Reference: 21 CFR 211.176, Penicillin contamination

It is not acceptable to release the product when other CGMP requirements have not been met. Although this section prohibits marketing of products found to be contaminated with penicillin, it does not sanction marketing of non-penicillin products based only on test results that show no detectable levels of such contamination. Other CGMP requirements must still be met. For example, there must still be adequate separation of facilities used for operations relating to penicillin production from facilities used for non-penicillins for human use.

Section 211.176 is an additive requirement to 21 CFR 211.42.(d) and 211.46(d), and does not mean that testing a product and finding it free from contamination renders the product marketable when produced under a reasonable possibility of contamination. Firms have inappropriately applied 211.176 as a means to market products that have been produced under adverse CGMP conditions.

FDA would not necessarily condone the shipment of potentially contaminated drugs that happen to test negative for penicillin. Drug products that are prepared, packed and held in a facility whereby they may have become contaminated or were in violation of CGMP, may be subject to regulatory action as adulterated (in the CGMP context). The question is not whether they were physically contaminated or even if they were "pharmacologically perfect". Rather, FDA has the enforcement discretion to decide whether to bring an action against such drugs. This prerogative would be based on factors such as violation significance, proposed corrections, and other case related circumstances. FDA's Office of Chief Counsel has indicated "To prevail on a charge of adulteration based upon a failure to conform to CGMP regulations, the government need not establish that any particular drug is actually deficient as a result." See U.S. vs. Western Serum Co., Inc., 498 F. Supp. 863 (D. Arizona 1980.)

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**On Stability: (Policy Questions Stability)**

***1) Are the CGMP regulations applicable to finished drug products that are repackaged into medical/surgical kits that contain both medical device and drug products?***

Reference: 21 CFR Sections 210.3(b)(12), Definitions, 211.100, Written procedures, deviations, 211.137, Expiration dating, 211.160 General requirements (Laboratory Controls), 211.165, Testing and release for distribution, 211.166, Stability testing, and 211.167, Special testing requirements; Compliance Policy Guide 7132c.06 (446.100), Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or other Manipulations

Yes. These operations, are by definition, part of manufacturing. Of particular concern are drugs that are packaged into trays or kits when the resulting package is sterilized then marketed for clinical use. The repackagers/kit assemblers should have data demonstrating that the sterilization process does not adversely affect the physical and chemical properties of the drug. The testing should be sensitive enough to detect any potential chemical reactions and/or degradation, and the test results should be compared with test values obtained prior to sterilization. Additionally, if the kits are sterilized with ETO (ethylene oxide) gas, ETO residues in the drug need to be controlled at safe levels. If the kits contain drugs that are subject to the new drug provisions in the Food Drug and Cosmetic Act, the sterile processing requires agency approval.

***2) Is an expiration date required on***

***sunscreen products?***

References: 21 CFR Sections 211.137, Expiration dating, and 211.166, Stability testing

Sunscreen products are drugs within the meaning of the Food, Drug and Cosmetic Act. As such, the Act requires that they be manufactured in conformance with the CGMP regulations. Hence, sunscreen products must be labeled with an expiration date that is based on appropriate stability studies. The only exception would be if the sunscreen product met the expiration dating exemption conditions in the CGMP regulations . Specifically, an expiration date is not required for human use OTC drugs that meet both of two conditions. They: (1) Do not bear dosage limitations; and, (2) are stable for at least 3 years as supported by appropriate stability studies.

Furthermore, investigators should be aware that, as stated elsewhere in this edition of Human Drug CGMP Notes, the Food and Drug Administration Modernization Act authorizes the agency to inspect all manufacturing and testing records related to OTC drugs.

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**Purely Speaking: (Impurity Issues)**

***1) What should investigators look for when inspecting a firm's cleaning validation program?***

Reference: 21 CFR 211.67, Equipment cleaning and maintenance; 21 CFR 211.100, Written procedures; 21 CFR 211.160, Laboratory controls; FDA Guide to Inspections of Validation of Cleaning Processes, July, 1993

The objective of cleaning validation is to ensure that a specific cleaning process will consistently clean to predetermined limits so as to prevent contaminants (product or cleaning process related) from adversely affecting the safety and quality of the next product manufactured.

As stated in the Guide to Inspections of Validation of Cleaning Processes, determine if firms have a written, well established and validated cleaning program. Basic steps include the development of a sensitive, accurate and precise analytical method for the determination of an acceptable limit, something necessary for any analytical test method developed in conformance with CGMPs. In addition, as discussed in the guide, determine if firms have and follow specific written procedures as to how cleaning will be performed, as well as how the cleaning validation will be conducted (including sampling procedures and analytical methods). Determine if the validation protocol addresses different sampling surface types, hardest to clean areas, and specific equipment, including utensils. FDA expects the validation studies will be completed in accordance with written protocols and that the final validation report will include the appropriate conclusions with management concurrence. Performing testing of cleaned equipment, in accordance with written procedures, would be consistent with 21 CFR 211.67(b).

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***2) Does FDA have impurities acceptance limits for cleaning validation and subsequent cleaning verification?***

Reference: 21 CFR 211.67, Equipment cleaning and maintenance; 21 CFR 211.60, Laboratory controls; 21 CFR 211.176, Penicillin contamination; International Committee on Harmonization (ICH) Guideline on Impurities in New Drug Substances, Q3A, May, 1997

FDA has always been concerned with the issue of contamination and cross contamination. Such contamination may include not only carry over from a previous product or residual cleaning solvents, but also detergents and surfactants.

Except for penicillin, FDA has not established standard acceptance limits for cleaning validation. Due to the wide variation in both equipment and products produced, it would be

unrealistic for the agency to determine a specific limit. In the CGMP context, however, firms need to establish limits that reflect the practical capability of their cleaning processes, as well as the specificity of the analytical test method.

We have found that some firms have incorrectly applied as their acceptance limit the 0.1% impurity identification threshold as discussed in both the ICH impurity guideline and the U.S.P. General Notices. This application of the 0.1% impurity threshold is inappropriate because the limit is intended for qualifying impurities that are associated with the manufacturing process or related compounds and not extraneous impurities caused by cross contamination. It is important that acceptance limits reflect the capability of the cleaning process.

When determining the acceptance limit, relevant factors generally include: (1) Evaluation of the therapeutic dose carryover; (2) toxicity of the potential contaminant; (3) concentration of the contaminant in the rinses; (4) limit of detection of the analytical test method; and, (5) visual examination. While we suggest that these factors be considered, relying only on visual examination would not be scientifically sound.

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### *3) Should non-pharmaceuticals be manufactured in common equipment with active pharmaceutical ingredients (APIs)?*

Reference: FD&C Act, Section 501(a)(2)(b); WHO Good Practices for the Manufacture and Quality Control of Drugs, June 1993

FDA has not specifically addressed this issue in a formal document. However, a fundamental tenet of current good manufacturing practice is that equipment does not contaminate the drugs -- that is, alter drug safety, quality or purity beyond established specifications. If you encounter instances in which non-pharmaceuticals are made in the same equipment as APIs, consider this basic tenet, and evaluate the suitability of using common equipment on a case by case basis.

Some non-pharmaceuticals pose unacceptable risks of cross-contamination and product mix-ups, and should therefore not normally be manufactured in common equipment with APIs. In some cases, in addition to separate equipment, it would be appropriate to use a separate facility for pharmaceutical chemical manufacturing.

This separation is an internationally recognized concept. For example, the World Health Organization (WHO) Guide to Good Manufacturing Practices discusses the use of separate facilities for the production of certain "non-pharmaceutical products." It adds that "the production of technical poisons, such as pesticides and herbicides," should not take place on the "premises used for the manufacture of pharmaceutical products."

As a general principle, the risks posed by unanticipated mix-ups or cross-contamination should be considered with particular emphasis on chemicals: (1) Known to pose any acute or long term toxicity concerns; or, (2) of incompletely characterized toxicity. Toxicological assessments normally include information such as acute data (e.g., LD50 determinations) using different routes of administration, mutagenicity, carcinogenicity, teratogenicity, sensitization, and irritation. Investigators should be aware that lack of toxicological assessments is not uncommon.

These risks are influenced by the nature and intended use of the drug products that will incorporate the API. For example, those risks may be of greater concern when the APIs will be used in dosage forms intended for: (1) Large doses, (2) long term therapy; (3) treating open wounds; (4) injection; or, (5) inhalation.

Even when an API manufacturer considers these issues, and determines that the non-pharmaceutical is “harmless” and can be made in common equipment with APIs, it is important that the manufacturer still follows CGMPs for APIs.

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**Gas What? (Policy Questions on Medical Gases):**

***1) Do CGMPs require validation of computerized air separation plants/units (ASU)? Is this new?***

Reference: 21 CFR 211.68(a) Automatic, mechanical, and electronic equipment.

Yes, those systems must be validated, per CGMPs. This is not new. Air separation plants or units (ASUs) take atmospheric air and, through a purification process of cleaning, compressing, and cooling, separate the air into the constituent gases - oxygen, nitrogen, and argon. ASUs are highly computerized, and have very few employees in attendance during operations, which are usually 24 hours a day, 7 days a week. Therefore, process validation, and especially validation of computerized processes, are essential to ensure proper functioning of the process and product quality.

The requirement for computerized process validation has been around since the last major revisions to the current good manufacturing practice regulations which occurred on September 29, 1978. Process validation was addressed in FDA's 1987 Guideline on General Principles of Process Validation. In addition, much has been written about this subject in the industry trade press. Therefore, both the requirement and the agency's expectations have been around for some time.

For yet unvalidated ASUs that have been in operation, i.e., shipping medical grade product, firms may apply, as a remedial measure, retrospective validation. (Product shipped from such unvalidated processes would be adulterated in the CGMP context.) As addressed in the 1987 validation guideline, a key principle in retrospective validation is that current operations are the same as past operations with respect to product specifications, the range of operating conditions, and equipment (ranges and changes). It is important that all changes and controls implemented since the original distribution of medical grade product in the retrospective period have been sufficiently documented. Otherwise, retrospective validation would not be scientifically sound, and older ASUs would need prospective validation, as would a new ASU that has not distributed medical grade product.

Investigators should refer to Fresh Air 98 for further information on the CGMP requirements for ASUs, focusing on process validation, especially computer systems validation. One other vital CGMP requirement is ensuring that a responsible individual of the ASU firm is the person who releases the finished drug product.

***2) SPECIAL REPORT - Health Care Facilities New Installations***

In 1996, 3 tragic deaths occurred in a Temple, Texas hospital during the installation of an oxygen storage tank. The hose used to connect the temporary oxygen supply to the hospital's oxygen system was not purged of a toxic cleaning solution, and the installing firm failed to detect the solution prior to its installation.

Health care facility installations usually occur at hospitals, nursing homes, clinics, etc. and usually involve the removal of the old supplier's storage tank and installation of a new storage tank.

FDA determined that some firms were failing to comply with the CGMPs for this type of operation. During the July 1996, Compressed Gas Association (CGA) meeting, these requirements were discussed. Further discussion occurred during the October 30, 1997, Clearwater CGA meeting, where specific CGMP requirements were outlined to assist the industry in achieving compliance.

Some firms incorrectly assumed that compliance with the standards addressed in NFPA (National Fire Protection Association) 50, Standard for Bulk Oxygen Systems at Consumer Sites, and 99, Health Care Facilities, was sufficient. However,

under the NOTICE section of both NFPA 50 and 99 is the statement, "Users of this document should consult applicable federal, state, and local laws and regulations."

Due to the possibility of exposing patients to a toxic solution at a health care facility, during your medical gas establishment inspections determine if the firm performs any health care facility installations.

Please refer to Fresh Air 98 for further information. Some areas of concern are the supplier audits of the contracted cleaning firm, any agreement with a contracted cleaning firm, the installing firm's cleaning procedures, finished product testing, written procedures, and process validation.

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**CGMP Sorites:**

Here is a CGMP logic puzzle, a particular form of deductive reasoning known as sorites. Sorites (pronounced soRYEtease) were made popular by Lewis Carrol, author of Alice in Wonderland. Sorites are an elliptic series of propositions arranged so that the predicate of the first premise is the subject of the next premise, and so on, until a conclusion can be obtained by uniting the subject of the first with the predicate of the last. This should be an entertaining way to expand and improve your reasoning skills, test your knowledge of CGMPs, and help you parse CGMP requirements .

First, here's an example by Lewis Carrol. The conclusion is given so you get the idea. Notice that the propositions are not in the sequential order necessary to obtain the conclusion.

(1) No experienced person is incompetent.

(2) John is always blundering.

(3) No competent person is always blundering.

Conclusion - John is not experienced.

Now, try the following CGMP sorites. Remember, the conclusion connects the subject and predicate from the first and last (which you need to determine) propositions by logically connecting the subjects and predicates of intermediate propositions.

(1) Written SOPs shall describe in sufficient detail the receipt, identification, storage, (e.g. quarantined/withheld from use) handling, sampling, testing and approval or rejection of components (i.e. raw materials). [ 21 CFR 211.80(a)]

(2) All released raw materials shall be first quarantined/withheld from use pending sampling, testing or examination. [21 CFR 211.84(a)]

(3) Quarantined/withheld raw materials, shall be stored until they have been tested or examined, as appropriate and released by the Quality Control Unit. [21 CFR 211.82(b)]

(4) Sample examination and testing includes the requirement that at least one test be conducted to verify the identity of each component. [ 21 CFR 211.84(d)(1)]

The conclusion appears after the final article in this issue.

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**Toward The Electronic Government:**

***1) More IT Acronym Finders***

The information technology (IT) lexicon is loaded with acronyms, and you will likely encounter them during your inspections and investigations. Here are two Internet sites that will help you decipher those acronyms.

1. At http:/www.mtnds.com/af the Mountain Data Systems in Estes Park, Colorado has an Acronym Finder for computer, telecommunications and military terms. The online database holds more than 50,000 of them.

Explanations are both informative and humorous. For example, the system defines ISDN to mean “Integrated Services Digital Network” and “I Still Don’t Know”. In case you’re not sure which meanings are legit, the humorous explanations are followed by the emoticon ":-)".

2. The second facility, operated by Whatis.com, Inc. at http://www.whatis.com has a database of over 1,400 terms, plus other information, such as data on “Every File Format In The World”. It presents an alphabetical list of computer file extensions, and their meanings. You might find this resource useful as you encounter electronic recordkeeping.

***2) Does an electronic signature time stamp need to be local to the signer or to a central network when an electronic batch record system spans different time zones?***

Reference: 21 CFR 11.50(a)(2); 62 Federal Register, No. 54, page 13453, March 20, 1997; final rule preamble to part 11, at comment paragraph 101.

The agency answered this question in the preamble to the final rule by saying “Regarding systems that may span different time zones, the agency advises that the signer’s local time is the one to be recorded.”

Recording the local time is important to not only clearly document the sequence of events in human terms, but also help authenticate an electronic signature and minimize chances of signer repudiation. For example, the local time stamp can be correlated with the whereabouts of the purported signer to help establish authenticity; if the person who supposedly signed the record was at a meeting, or otherwise unable to sign the record at the time of signature execution, the time stamp would help show that an imposter executed the signature. A firm could then initiate an appropriate investigation.

Part 11 does not, however, prohibit a firm from supplementing the local time stamp with the time stamp of a remote central server that may be in a different time zone from the signer. Where dual stamps are recorded, though, it is important that the electronic record clearly indicate which one is local to the signer.

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**Special Report**

***Prevention/transmission of bovine spongiform encephalopathy (bse) in the use of bovine derived ingredients in drug products.***

Bovine Spongiform Encephalopathy, or BSE, is the name of a fatal brain disease in beef and dairy cattle which is known to exist in several countries including the United Kingdom. The disease also has been given the nickname "Mad Cow Disease". However, the cows are not mad. Rather, they suffer from a progressive neurological disorder leading to loss of muscular coordination and subsequent death. The causative agent of this disease is thought to be transmission from a related disease in sheep called "scrapie", through feeding of rendered sheep in meat and bone meal to young beef calves. Humans also can suffer from encephalopathies, and there may be an epidemiologic association between BSE and a form of a human encephalopathy known as Creutzfeldt-Jakob (nv-CJD) reported in England. The causal agent in the association is unknown, but suspected to be a protein material called "prion". This causative agent or “prion” is extremely resistant to heat and to normal sterilization processes. It does not lead to detectable immune responses or inflammatory reaction in the animals carrying the disease, nor is there a validated assay method for its detection. One study (Veterinary Record 1997, 141, 643-649) reported that only a process involving exposure to hyperbaric steam left meat and bone meal samples with no detectable infectivity.

Based on this association and the resistance of this “prion”, both the U.S. Department of Agriculture (USDA) and FDA have developed rules and guidance to prevent its occurrence in

the United States through a process of reducing the risks involved with transmission.

At the present time, according to the Animal and Plant Health Inspection Service of the USDA, based on its active and continuing surveillance efforts since 1989, BSE has not been detected in the United States. Furthermore, USDA has identified and maintains a list of countries where BSE has been diagnosed (Title 9 Code of Federal Regulations) and has placed restrictions on imports from these countries.(Federal Register (FR) Vol. 63 No.3 dated Tues, Jan 6, 1998). FDA's Center for Veterinary Medicine also has issued (FR, Vol. 62. No. 108 dated Thursday, June 5, 1997) restrictions on the types of animals/organs that can be used in ruminant feed to maintain the absence of BSE in the U.S. Furthermore, the World Health Organization (WHO), has developed categories listing tissues having increasing risk of containing the "prion" thought responsible for BSE (WHO report dated Nov.12-14, 1991). There are three categories listing high infectivity, medium infectivity, and low infectivity.

From 1993 to 1996, the FDA Commissioner issued a series of letters to industry addressing the need to reduce the risk of BSE transmission. The letters recommended that the drug industry:

(1) Investigate the geographic source of any bovine or ovine material (generally neural or glandular tissue and tissue extracts) used in their products;

(2) develop a plan to ensure with a high degree of certainty such materials are not from BSE countries or from scrapie-infected sheep flocks, either foreign or domestic;

(3) maintain traceable records for each lot of bovine-derived materials in their products and each lot of FDA regulated product using these materials, and identify all countries where the animals used to produce the material have lived; and,

(4) maintain copies of the records identified above for FDA regulated products that are manufactured with bovine derived materials at foreign sites, or by the foreign manufacturers.

FDA also has in effect Import Alert (17-04) for detention of bulk shipments of high risk bovine tissues and tissue derived ingredients from BSE countries.

Drug manufacturers should be aware that regulated products intended for administration to humans and manufactured with bovine-derived materials from cattle that have at any time been in BSE-countries may be adulterated under Section 501(a)(2)(B) of the Federal, Food, Drug, and Cosmetic Act. There are some exceptions including those involving gelatin for oral consumption or cosmetic use based on additional cautions. (See FDA Gelatin Guidance for Industry, Sept. 1997)

At least one manufacturer of a drug product has investigated its manufacturing process for inactivation/removal of infectivity causing BSE which has been reported in Biologicals (1996)24,103-111. This type of action may be a prudent step for drug manufacturers who use bovine or ovine raw material to further reduce the risk of transmission and address the issue of BSE safety of their drug products.

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**Conclusion to CGMP Sorites:** Written SOPs shall describe at least one test to be conducted to verify the identity of each component of drug product. ( "Testing" in 21 CFR 211.80(a), includes component identity tests.) Other component control requirements still apply, of course; this sorites helps you parse this particular requirement. [P.S. Don't let John write your SOPs.]

P. Motise 6/1/98
DOC ID CNOTES68.w60

## *FAX FEEDBACK*

TO: Paul Motise, HUMAN DRUG CGMP NOTES, HFD-325
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__not very: __ somewhat; __ very; __ extremely useful to my inspectional/compliance activities.

Here's my question regarding _____
_____
_____
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Future editions of HUMAN DRUG CGMP NOTES should address the following CGMP questions/issues:
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